

Aplasia and leukaemia following chloroquine therapy

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Summary

Three patients with aplastic anaemia following chloroquine therapy are described. In two, chloroquine had been administered in large doses over a long period. One of them subsequently developed acute myeloblastic leukaemia. The third received only a small dose and pancytopenia with aplasia followed three weeks after ingestion of the drug. The mechanism(s) of chloroquine-induced marrow injury is not known. A parallel to chloramphenicol-induced blood dyscrasias is drawn, but remains unproved.

BONE marrow aplasia with pancytopenia or some form of bone marrow injury, resulting in isolated cytopenias can result from many drugs in current use. A positive history of drug exposure can be obtained in more than 66% of patients with aplastic anaemia (Vincent and de Gruchy, 1967). Chloramphenicol, phenylbutazone, mephenytoin, sulphonamides and gold compounds are the drugs most commonly reported as causing marrow aplasia.

It is well known that certain agents capable of producing aplastic anaemia in man can also cause leukaemia (Dougan and Woodliff, 1965). The development of leukaemia in the course of aplastic anaemia is of considerable interest. Aplastic anaemia without known cause may be premonitory of acute leukaemia (Saarini and Linmann, 1973; Nagaratnam, 1976) or aplastic anaemia with a known cause may develop into acute leukaemia. Chloramphenicol is a commonly cited cause of acquired aplastic anaemia, and case reports of acute myelocytic leukaemia following chloramphenicol-induced aplasia have been published (Mukherji, 1957; Brauer and Damashek, 1969). There seems therefore to be a pathogenic relationship between aplastic anaemia and acute myelogenous leukaemia. It is reasonable to consider any agent that is potentially myelotoxic as potentially leukaemogenic.

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Three patients are described who initially presented with aplastic anaemia, one of whom later developed acute myelogenous leukaemia. Two had taken chloroquine for many months and the third developed symptoms some little time after ingestion of the drug. The authors believe that chloroquine was involved in causing the bone marrow injury in these patients.

Case no. 1

A 60-year-old man was admitted to his local hospital in July 1973 for investigation of anaemia which followed chloroquine therapy for discoid lupus erythematosus. He had been taking chloroquine for several months. He had no ocular, otic or muscular symptoms. Physical examination showed marked pallor. There was no organomegaly or lymphadenopathy. A complete blood count showed a haemoglobin level of 4.4 g/dl, and haematocrit of 15% (Table 1). The total white blood cell count was $8.4 \times 10^9/l$, the differential count was normal. The platelet count was $277 \times 10^9/l$. The ESR (Westergren) was 152 mm in 1 hr. The reticulocyte count was 0.4%. He was transfused on two occasions and treated with parenteral iron and subsequently with oral iron, prednisolone and folic acid. Marrow aspiration revealed marked hypoplasia. He was transfused again in September 1973 and received further transfusions in May and July 1974.

In December 1974 he developed fever with disordered sensorium and a diagnosis of cerebral malaria was made. He was treated with intravenous chloroquine, dexamethasone and penicillin. The haemoglobin on this occasion was 8 g/dl; white cell count $4.2 \times 10^9/l$, with a normal differential. He was discharged after receiving several blood transfusions.

He was re-admitted in September 1975 with a swelling of his right arm and fever of one month's duration. On examination he was very pale and there was generalized lymphadenopathy. The liver and

spleen were not palpable. The results of the haematological investigations are shown in Table 1. Bone marrow at this stage showed a marked predominance of undifferentiated peroxidase negative blast cells some of which showed myelomonocytoid features. Megakaryocytes were scanty.

Comment: This patient developed anaemia and reticulocytopenia following large doses of chloroquine over several months for discoid lupus erythematosus. Chloroquine was discontinued and he was treated with haematenics and transfusions until 18 months later when he had cerebral malaria and was once again treated with chloroquine. In September 1975, 27 months after he first came under observation, he was found to have acute myeloblastic leukaemia.

Case no. 2

A 29-year-old female was examined for severe anaemia at the General Hospital, Batticaloa, in September 1975. She gave a history of continued fever accompanied by chills and rigors of one month's duration. She had been treated with chloroquine for malaria on several occasions and had been on prophylactic chloroquine for several months. When seen, she was febrile, severely anaemic and had a palpable spleen. A blood smear showed anisopoikilocytosis and hypochromia. The haemoglobin was 2.5 g/dl, and the total white blood cell count, $3.0 \times 10^9/l$. The ESR (Westergren) was 122 mm in 1 hr. She was treated with blood transfusions and parenteral iron. She became afebrile a few days later. No antibiotics had been given.

A few days after discharge she was re-admitted with high fever. She was extremely pale. The liver was palpable three fingerbreadths below the right costal margin and the spleen two fingerbreadths

below the left costal margin. She was treated with ampicillin and prednisolone. The following day the fever subsided. On discontinuation of the prednisolone her fever returned and the drug had to be re-introduced. Her haemoglobin was 3.5 g/dl, white cell count $1.8 \times 10^9/l$ with a differential count of neutrophils $0.25 \times 10^9/l$, lymphocytes $1.48 \times 10^9/l$, eosinophils $0.018 \times 10^9/l$ and monocytes $0.054 \times 10^9/l$. The platelet count was $90 \times 10^9/l$. Malarial parasites were not seen on peripheral blood smears. The reticulocyte count was 1.4%. The blood and stool cultures were sterile. She was transfused with 4 pints of blood.

She was then transferred to the General Hospital, Colombo. On admission, she was severely anaemic and was afebrile. Physical examination revealed no abnormalities other than a palpable liver and spleen. The haemoglobin was 4.4 g/dl and the total white blood cell count was $1.8 \times 10^9/l$. The platelets numbered $12.0 \times 10^9/l$. Serum folate level was 5.3 ng/ml and B_{12} 1500 pg/ml. The reticulocyte count was 0.1%. LE cell preparation was negative. Bone marrow aspiration resulted in a dry tap and a trephine biopsy of the iliac crest showed an increase of fat spaces in the marrow with marked diminution of erythropoiesis and scanty megakaryocytes. Erythropoiesis was normoblastic. There were islets of cells with an increase in the blast cells (Fig. 1a, b).

She was treated with high doses of prednisolone and oxymetholone, antibiotics and several blood transfusions until her death. There was no post-mortem.

Comment: This patient has been treated for malaria on several occasions and had been on malarial prophylaxis for several years. The diagnosis was one of aplasia. There were, however, islets of cells with some increase of blast cells.

TABLE 1. Haematological data of patient 1

	July 1973	December 1974	September 1975
Haemoglobin g/dl	4.4	7.4	6.1
Leucocyte count $\times 10^9/l$	8.4	4.2	20.8
Differential count $\times 10^9/l$	N, 5.6 L, 2.3 E, 0.34 M, 0.17	N, 2.5 L, 1.34 E, 0.18 M, 0.18	Blast cells 15.8 L, 4.4 M, 0.6
Platelets $\times 10^9/l$	277	—	19
ESR mm/hr	152	110	151
Reticulocytes %	0.4	0.1	—

N, neutrophils; L, lymphocytes; E, eosinophils; M, monocytes.

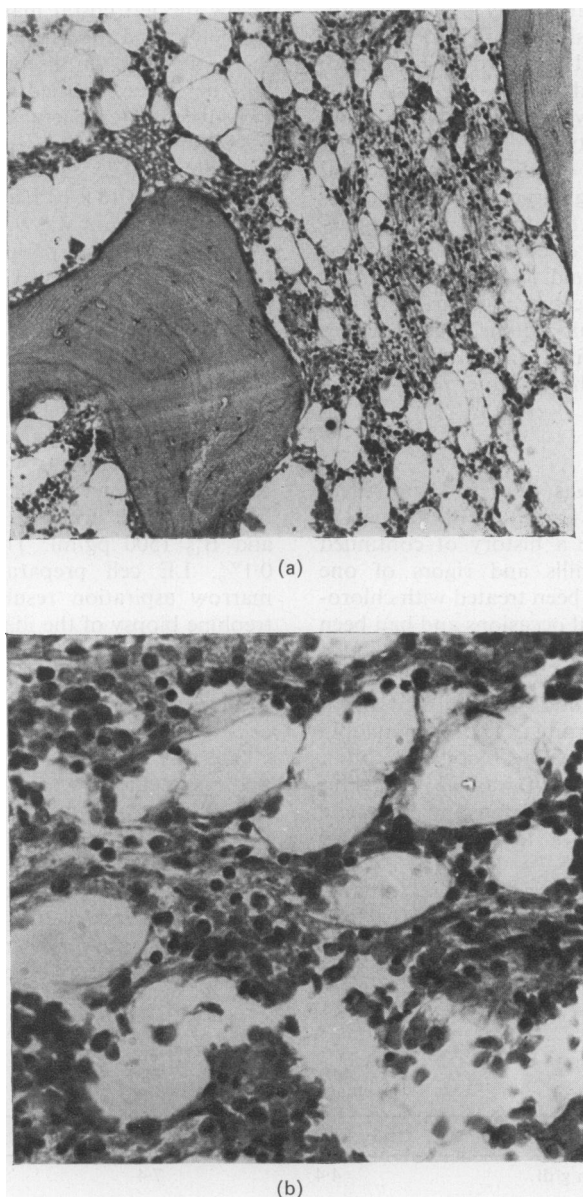


FIG. 1 (a). Iliac crest biopsy of patient 2 showing increase of fat spaces with islets of cells (HE, $\times 100$); (b) same, with islets of cells and fat spaces (HE, $\times 200$).

Case no. 3

A 22-year-old male developed fever with chills and rigors in November 1975. Malaria was diagnosed and he was treated with chloroquine and was asymptomatic on discharge. Three weeks later, in December, he suddenly developed fever and bleeding gums. There was no history of jaundice or any prolonged

illness and he had not been on any prolonged drug therapy. He had never handled insecticides.

On admission he was extremely pale and there was systolic murmur in the pulmonary area. The haemoglobin was 2.7 g/dl, and white cell count was $3.6 \times 10^9/l$. He was transfused with 3 pints of blood. In January 1976 he presented with bleeding gums,

weakness and occasional vomiting. Haematological investigations revealed a haemoglobin of 2.3 g/dl, white blood cell count of $4.2 \times 10^9/l$, and a differential of $1.18 \times 10^9/l$ neutrophils, $2.92 \times 10^9/l$ lymphocytes, and $0.08 \times 10^9/l$ monocytes. The platelets numbered $120 \times 10^9/l$. The ESR (Westergren) 110 mm in 1 hr. Reticulocyte count $0.2/mm^3$, bleeding time >10 min and clotting time 3 min. He was given blood transfusions.

He was transferred to the General Hospital Colombo, and on admission he was extremely anaemic with extensive dermal haemorrhages. There were haemorrhages in the ocular fundi. Haemoglobin level was 3.5 g/dl, haematocrit 21%, white cell count $5.0 \times 10^9/l$, platelets $21.0 \times 10^9/l$, bleeding time of >20 min and serum bilirubin of 1.0 ng/dl. Peripheral blood film was negative for malarial parasites. A marrow aspirate showed a very hypocellular marrow. Iliac crest biopsy showed an extremely fatty marrow with very little haemopoietic tissue (Fig. 2). His B_{12} level was 230 pg/ml; and folate 4.2 ng/ml. He was treated with high doses of

steroids, and blood transfusions. He died 3 months later.

Comment: This young male had had a short course of chloroquine. He had not taken any other drugs. Anaemia with neutropenia followed three weeks' ingestion of the drug; and marrow later revealed aplasia.

Discussion

Chloroquine had been taken by all three patients, two of whom had taken it in large doses over a long period, and the third in a relatively small dose. All developed aplasia of the bone marrow. There was no history of any other drug or chemical agent that could be incriminated. All three patients were from areas endemic for malaria.

Neva (1967) stressed the importance of making a clear distinction between potential hazards of long-term treatment of arthritis and collagen diseases with chloroquine, in contrast to a more limited use of the drug as an anti-malarial. He feels that much confusion can result from papers dealing with chloroquine toxicity if it is not made clear that malarial prophylaxis requires the drug in doses of 0.5 g weekly and acute malaria requires it in a dose of 2.5 g daily for two to three days. However, in contrast to this, chloroquine-induced ocular, otic and muscular damage followed when the drug was given in doses of 0.25–1 g daily for 4–6 months.

The relationship between chloroquine and bone marrow injury is still uncertain. Agranulocytosis is a blood dyscrasia frequently reported as being due to chloroquine and hydroxychloroquine (Propp and Stillman, 1976; Polana, Cats and Van Olden, 1965; McDuffie, 1965). According to Propp and Stillman (1967) the manufacturers of hydroxychloroquine have had in their files some unpublished cases of blood dyscrasias associated with this drug: one of aplastic anaemia (fatal), one of thrombocytopenia (fatal), one of agranulocytosis and one of aplastic anaemia.

The mechanism of bone marrow injury due to drugs and other agents remains unclear. Perhaps, in this respect, chloramphenicol is a drug that has been most extensively studied. According to Yunis and Bloomberg (1964) and Yunis (1975), two main forms of aplasia following chloramphenicol therapy could be identified. In one, the onset is acute, it is dose-related and frequently the marrow is normocellular but exhibits vacuolization of erythroblasts and granulocytic precursors. There is moderate anaemia and reticulocytopenia. Unless the dosage is remarkably high, this type of aplasia is reversible when the drug is discontinued (Brauer and Damashek, 1969). The other is of late onset and may not be dose-related. There is hypoplasia or severe aplasia of the marrow and the

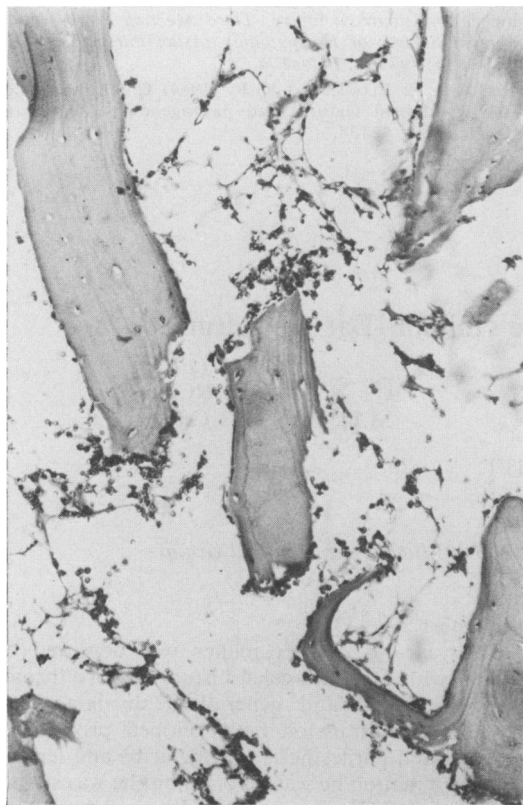


FIG. 2. Iliac crest biopsy of patient 3 showing severe marrow aplasia (HE, $\times 100$).

manifestations of marrow depression occur weeks or months after the drug has been stopped. In the former, the current evidence is that the reversible bone marrow suppression following chloramphenicol results from inhibition of mitochondrial protein synthesis. In the other, there is a strong suggestion of a stem cell lesion. The rare occurrence of this complication is suggestive of individual predisposition.

It is tempting to use some of these signs to explain the findings in the three patients following the use of chloroquine. It would appear that patients 1 and 2 belong to the dose-related categories. In patient 1, the primary effect of the drug was anaemia, it was only after the further use of the drug months later that the condition was aggravated. In patient 3, there is no relationship to dose and he had severe aplasia which occurred three weeks after the drug had been administered.

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Cytomegalovirus infection and the Guillain-Barré syndrome

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Summary

A fatal case is described of the Guillain-Barré syndrome due to cytomegalovirus infection, which was associated with hepatitis, myocarditis and viral pneumonia.

Previous cases, which have usually run a benign course, are reviewed. Attention is drawn to the possible adverse effect of steroid therapy.

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Case report

A 22-year-old cabinet maker was admitted to hospital with a three weeks' history of sore throat, cough, headache and generalized myalgia. Two weeks before admission he developed progressive weakness and paraesthesiae of the arms and legs.

On examination he was afebrile, but he was sweating profusely. There was marked generalized lymphadenopathy and the fauces were mildly injected. He had a persistent tachycardia of 120–140/min.